Scientific Abstract

In this phase I/II clinical trial, increasing doses of a DNA plasmid called Synchrovax BPL Vaccine will be injected intralymphnodally in patients with stage IV breast carcinoma. The primary endpoints of the study are to define the toxicities and the MTD (if any). Secondary endpoints include determining whether there has been an immune response to the DNA vaccine encoding NY-ESO-1 epitopes. Synchrovax BPL Vaccine contains a mini-gene that encodes a 179 amino acid polypeptide, embedded in which are two copies of the HLA-A2 specific CTL epitope, NY-ESO-1 (157-165) and one copy of the 104-amino acid protein fragment NY-ESO-1 (77-180). Although measurable disease will not be a requirement for study entry, clinical responses will be assessed in patients with measurable disease. The primary hypothesis of this study is that the Synchrovax BPL Vaccine, a plasmid DNA vaccine, is safe and tolerable when used for the treatment of stage IV breast carcinoma. It is also hypothesized that use of the vaccine will result in the generation of an immune response directed against NY-ESO-1 expressing tumor cells.

The population to be treated with the DNA vaccine includes patients with stage IV breast carcinoma without brain metastases who are HLA-A2 positive (the epitopes encoded by the plasmid are restricted to HLA-A2). Tumor expression of NY-ESO-1 and β2 microglobulin will also be required for entry. Eighteen eligible patients will be enrolled sequentially to treatment cohorts (six patients per treatment cohort) of 500 μg, 1000 μg, and 1500 μg of Synchrovax BPL Vaccine. A fourth cohort of nine patients will receive the Maximum Tolerated Dose or optimal dose of Synchrovax BPL Vaccine. The vaccine will be delivered by continuous infusion using a miniaturized pump via a catheter inserted into a groin lymph node under ultrasound guidance. The continuous infusion over 96 hours, followed by removal of the catheter and a nine-day rest period, comprises one cycle lasting two weeks. Each study patient will undergo four cycles of infusion over eight weeks, which constitutes one course of therapy. Proper catheter position will be verified by ultrasound on the first day of infusion and at the end of the fourth day of infusion of each cycle. The portable pump will be worn on the belt and patients will be permitted to ambulate during the four-day infusion. A disease evaluation will be carried out after eight weeks, or one complete course of treatment. Evaluations to assess immunological response include analysis of antigen-specific CTL response using a quantitative peptide-specific flow cytometry procedure (Tetramer Assay) and a quantitative intracellular staining assay. Both assays will be performed before, during, and after each treatment course.

Eligible patients who are HLA-A2 positive will have a staging workup consisting of CT scans of chest, abdomen and pelvis prior to initiation of therapy to define the extent of their disease. If clinical symptoms suggest brain metastases, patients will also have an MRI of the brain. The tests that showed evidence of disease will be repeated at the end of a course of treatment during week eight. Patients with evidence of tumor regression may undergo one subsequent course of therapy.

No life threatening side effects or deaths were seen with previous tests of vaccines employing peptides or dendritic cells pulsed with peptides or tumor lysates injected intralymphnodally in patients with metastatic melanoma. The toxicities related to injection of DNA vaccines subcutaneously or intravenously included headache, fevers, weakness, arthralgias and a rash that

spontaneously resolved without therapy. In a recent clinical trial of a DNA plasmid vaccine expressing tyrosinase, no severe or life-threatening side effects were observed. In animal testing, intranodal administration of Synchrovax BPL Vaccine was not associated with any deleterious effects.

Because mRNA transcripts of NY-ESO-1 have been found in the ovary, an autoimmune reaction is possible in this area. However, since NY-ESO-1 protein expression has never been observed in the ovary, the antigen is strictly tumor specific and should constitute a safe immunogen. Swelling of the joints with inflammation, pain, rashes and abnormalities of kidney and liver function might also occur.

It is possible that there might be damage to the lymph node into which the DNA plasmid vaccine infusion is given. The lymph node might become edematous or tender, or bleeding may occur. This has been shown to be temporary, with the lymph node returning to normal after the injections. The plastic catheter will be inserted in a sterile manner into the lymph node, but infection at the injection site might also occur.